Prognostic subclassifications of T1 cutaneous melanomas based on ulceration, tumour thickness and Clark's level of invasion: results of a population-based study from the Swedish Melanoma Register

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Bulleted statements: Previous studies about prognostic factors for thin melanoma shows the impact of tumour ulceration, tumour thickness and Clark's level of invasion. The present authors verify the importance of the prognostic factors above and also suggest better ways to combine these factors to create distinct subgroups. Further, this study includes a large population-based group of patients with more than 15 years of follow-up data and the result gives accurate information about prognosis for the patient group.

Abstract

Background: Survival and prognostic factors for thin melanomas have been relatively little studied in population-based settings. This patient group account for the majority of melanomas diagnosed in western countries today and better prognostic information is needed.

Objective: The aim of this study is to use established prognostic factors such as ulceration, tumour thickness and Clark's level of invasion for risk stratification of T1 cutaneous melanoma.

Methods: During 1990-2008, the Swedish Melanoma Register (SMR) included 97% of all melanomas diagnosed in Sweden. All together 13 026 patients with T1 melanomas in clinical stage I were used for estimating melanoma-specific 10- and 15-year mortality rates. Cox regression model was used for further survival analysis on 11 165 patients with complete data.

Results: Ulceration, tumour thickness and Clark's level of invasion all showed significant independent long-term prognostic information. By combining these factors the patients could be subdivided into three risk groups: a low risk group (67·9% of T1 cases) with a 10-year melanoma-specific mortality rate of 1·5% (1·2-1·9%), an intermediate risk group (28·6% of T1 cases) with a 10-year mortality rate of 6·1% (5·0-7·3%) and a high risk group (3·5% of T1 cases) with a 10-year mortality rate of 15·6% (11·2-21·4%). The high- and intermediate risk group accounted for 66% of melanoma deaths within T1.

Conclusions: Using a population-based melanoma register and combining ulceration, tumour thickness and Clark's level of invasion three distinct prognostic subgroups were identified.

Key words: thin cutaneous malignant melanoma; mortality; prognostic factors; population-based.

Abbreviations used: SMSG: Swedish Melanoma Study Group; **SMR:** Swedish Melanoma Register; **CMM:** Cutaneous Malignant Melanoma; **AJCC:** American Joint Committee on Cancer; **ALM:** Acral Lentiginous Melanoma; **HR:** Hazard Ratios; **CI:** Confidence Intervals; **QCR:** Queensland Cancer Registry; **SEER:** Surveillance, Epidemiology, and End Results; **NSW:** New South Wales; **CMMR:** German melanoma register; **PLG:** Pennsylvania pigmented lesion group; **SMU:** Sydney melanoma unit.

1. Introduction

Since 1990, the Swedish Melanoma Study Group (SMSG) has prospectively gathered data concerning diagnosis, treatment, and follow-up on all Swedish cases of Cutaneous Malignant Melanoma (CMM). The data is collected and registered at the six regional oncology centres in Sweden and transferred to the national database, the Swedish Melanoma Register (SMR) in Linköping. A first report on CMM in Sweden (1990-1999) has been published [1]. Since a majority of melanomas diagnosed in many countries are thin (≤1 mm), further studies concerning this large subgroup of melanoma patients are motivated. In the American Joint Committee on Cancer (AJCC) 2009 the mitotic index has been added as prognostic factor [2] and the research of other new factors are in progress [3,4]. However, there are a few studies from Germany, Australia, and USA [4-10] that indicate that the previous AJCC 2002 melanoma staging [11] could be further refined for thin melanomas by simply combining the traditional prognostic factors in alternative ways. Due to its size and being population-based, the SMR is ideal when exploring new risk stratifications in thin melanomas. The aim of this study is to use established prognostic factors such as ulceration, tumour thickness and Clark's level of invasion for risk stratification of T1 cutaneous melanoma.

2. Materials and methods

During the time period 1990-2008, 30 157 patients with primary CMMs were reported to the SMR. The mean annual coverage rate was 97% (range 93-99%) compared to the Swedish National Cancer Register, to which reporting of all new malignancies is mandated by Swedish law [12]. The current registration is population-based and nationwide. All cases are registered with a unique patient identification-number which facilitates record linking.

From the 30 157 patients, 13 488 (44·7%) patients had T2-T4 tumours and 1183 (3·9%) patients had no information about tumour thickness and were both excluded. The remaining 15 486 patients (51·4%) had T1 melanoma (≤1 mm thick) as their first invasive diagnosis. Patients with previous CMMs diagnosed before 1990 were identified from the Swedish Cancer Register and excluded (231 patients). From the T1 patient group, 2229 patients were excluded because they were either not in clinical stage I at diagnosis (127 patients) or information about clinical stage at diagnosis (2102 patients) was lacking, since

this data was not regularly registered in one region. Data on the remaining 13 026 patients in clinical stage I was used in a univariate Kaplan-Meier analysis of melanoma-specific 5-, 10- and 15-year mortality rates. Further a Cox analysis for prognostic factors was undertaken on 11 165 patients aged 15-89 years having other types than Acral Lentiginous Melanoma (ALM) and with the tumour localised other than palm/subungual. The ages 15-89 were chosen because children with melanoma seem to have different outcomes from adults [13] and the cause of death of patients aged 90+ could be uncertain due to co-morbidities. ALM type and melanomas localised to palm/subungual were excluded in order to avoid potential errors in the measure of tumour thickness.

The following clinical variables were studied: age at diagnosis, gender and tumour site. Histopathological characteristics of the primary tumour including tumour thickness, Clark's level of invasion, presence/absence of ulceration and histogenetic type were registered. Histopathological data was reported directly from the pathology department's database. Data on cause of death until December 31, 2009 was obtained from the Swedish Cause of Death Register and was used to calculate the melanoma-specific mortality rate. Patients having a second CMM during the study period were censored at the point in time of the second diagnosis.

Excision margin used was 1 cm except for a small cohort of CMM with tumour thickness ≥0·8 mm operated 1990-1991 with 2 or 5 cm wide excision margins due to an ongoing study at that time [14]. According to the Swedish National Guidelines for CMM, sentinel node biopsy was not recommended for melanomas ≤1 mm before 2007. However, sentinel node biopsies were performed in 91 cases with positive results in 5. Shave biopsies and other similar procedures are not recommended by the Swedish National Guidelines for CMM.

2.1. Statistical analysis

Survival time was calculated from the date of diagnosis (date of diagnostic biopsy or date of pathology report) to the date of event or to the date of censoring. In the analysis, death from melanoma is considered as the primary event. Censoring was made at the time point of; patient emigrating, patient diagnosed with a second CMM during the study period, patient died from causes other than melanoma or end of follow up. Melanoma-specific mortality rates and confidence intervals were estimated using the method of Kaplan and Meier [15]. Cox´s proportional hazard regression was used to assess the independent

prognostic contribution of clinical variables, either alone, or after adjustment for other clinical variables. The prognostic impact of clinical variables was expressed as Hazard Ratios (HR) with 95 percent Confidence Intervals (CI).

For comparing multivariate Cox models, the likelihood ratios and degrees of freedom between models was evaluated with $\chi 2$-tests. Statistical significance was indicated by *p*-values below 0·05. In order to simplify the Cox-analysis, some categories not being significantly different were merged. All potential interactions between different variables were investigated.

The results from the Cox-analyses combined with results of melanoma-specific mortality rates from Kaplan-Meier were used to identify prognostic subgroups. In the text and the tables, 95% CI are shown in parentheses. All statistical analyses were performed by using SAS 9·2.

3. Results

During a median follow up time of 6·6 years (range 0-20 years), 311 (2·4%) patients died from their melanoma. Within the follow-up period, 1731 (13·3%) patients died of causes other than melanoma. There were 314 patients (2·4%) with a second melanoma diagnosis within the study period. An additional 27 (0·2%) patients were censored due to emigration. The median age at diagnosis was 58 years, the median thickness was 0·6 mm and 55% of the patients were women.

-Insert Table 1 about here-

Melanoma-specific mortality rate data from the SMR are presented in Table 1. The overall 10- and 15-year melanoma-specific mortality rates were 3·4% (3·0-3·8%) and 4·4% (3·9-5·0%), respectively. The melanoma-specific mortality rates for the very thin (≤0·5 mm) compared to the thickest (>0·75 mm) varied from 1·9% (1·0-3·7%) to 6·6% (5·6-7·8%) at 10 years and from 3·2% (1·6-6·4%) to 8·9% (7·5-10·6%) at 15 years.

In univariate Cox analysis of mortality, the three most dominant factors were tumour thickness ($\chi 2$=103·2, df=2, *p*<0·0001), ulceration ($\chi 2$=83·2, df=1, *p*<0·0001) and Clark's level of invasion ($\chi 2$=74·6, df=2, *p*<0·0001) (Table 2). The largest effect estimates were observed for melanoma thickness >0·75 mm versus ≤0·5 mm group (HR: 4·7, 95% CI 3·4-6·5), ulceration versus non-ulceration (HR: 4·5, 95% CI 3·3-6·2) and Clark level IV-V versus Clark level II (HR: 4·4, 95% CI 3·0-6·3).

-Insert Table 2 about here-

In the multivariate Cox analysis ulceration ($\chi 2$=46·7, df=1, p<0·0001), tumour thickness ($\chi 2$=29·4, df=2, p<0·0001) and Clark's level of invasion ($\chi 2$=12·3, df=2, p=0·002) were still the most important prognostic factors (Table 2). The highest hazard ratios were observed for ulceration versus non-ulceration (HR: 3·2, 95% CI 2·3-4·4), melanoma thickness >0·75 mm versus ≤0·5 mm group (HR: 2·8, 95% CI 1·9-4·1) and Clark IV-V versus Clark II (HR: 2·1, 95% CI 1·4-3·3). In a further multivariate Cox analysis of all potential interaction effects (data not shown), there was a significant interaction between tumour thickness and ulceration ($\chi 2$=6·9, df=2, p=0·03). This interaction indicates that tumour thickness was a less important prognostic factor when the melanoma was ulcerated (HR: 0·8 for >0·75 mm versus ≤0·5 mm group, 95% CI 0·3-1·9) compared with non-ulcerated melanomas (HR: 3·5 for >0·75 mm versus ≤0·5 mm group, 95% CI 2·3-5·4).

The multivariate analysis confirmed the great influence of ulceration, tumour thickness and Clark's level of invasion on melanoma-specific mortality. Thus, we estimated the 10-year melanoma-specific mortality rate in each patient group defined according to these three tumour characteristics (Table 3).

-Insert Table 3 about here-

Using the results presented in Table 3 we divided the T1-melanomas into three risk groups: a low risk group of non-ulcerated Clark II-III ≤0·75 mm melanomas (67·9% of T1 cases) with a 10-year melanoma-specific mortality rate of 1·5% (1·2-1·9%); an intermediate risk group of melanomas that were non-ulcerated >0·75 mm; or non-ulcerated Clark IV-V; or ulcerated Clark II ≤0·75 mm (28·6% of T1 cases) with a 10-year melanoma-specific mortality rate of 6·1% (5·0-7·3%); and a high risk group consisting of all ulcerated T1 melanomas except Clark II ≤0·75 mm (3·5% of T1 cases) with a 10-year melanoma-specific mortality rate of 15·6% (11·2-21·4%). Fig.1 shows the cumulative melanoma-specific mortality for the three risk groups.

-Insert fig.1 about here-

4. Discussion

The authors analysed all melanomas registered in the SMR 1990-2008, a large unselected material representing the total Swedish population. The benefits of using large population-based materials are evident from a review of published survival data concerning thin melanomas. We have transformed and

used this data as 10-year melanoma-specific mortality rates. The data from the current study (SMR), Queensland Cancer Registry (QCR) [5], Surveillance, Epidemiology, and End Results (SEER) [6,7] and New South Wales (NSW) [10] can be categorised as population-based while other cohorts are either multi- or single institution data; AJCC 2002 [11,16], AJCC 2009 [2], the German melanoma register (CMMR) [8], Pennsylvania pigmented lesion group (PLG) [6] and Sydney melanoma unit (SMU) [10].

-Insert Table 4 about here-

The 10-year melanoma-specific mortality rates of T1a andT1b melanomas are much lower in the population-based materials SMR, QCR and SEER compared to the high mortality rates of compiled or institutional based materials as reported in the AJCC 2002 and AJCC 2009 data (although using other criteria for T1a and T1b). Our findings thus confirm the findings of Gimotty et al. [7] who validated the AJCC 2002 classification and found that it was suitable for constructing stages, but was imperfectly calibrated to the US population, since the survival rates in the AJCC material were much lower than in the US population [7]. This would have been due to that large specialised institutions contribute to the AJCC database with a higher proportion of patients with poor prognosis since patients with T1 melanomas and recurrence are referred to those institutions for further treatment. Similar conclusions were drawn in a European population-based study from the Netherlands [17]. The data of T1 melanomas from the population- based NSW has an equally low mortality rate as the SMR data, in contrast to the institutional SMU data with high mortality rates which are similar to that of AJCC 2002. The latter fact is not surprising, considering that the SMU contributed with 8 667 of the 17 600 cases in the AJCC 2002 database.

SMR data indicate that the original thickness cut off value (0·76 mm) defined by Breslow [18] still seems to have a significant impact on the prognosis of T1 melanoma. Clark et al. [19] demonstrated that almost all melanomas ≤0·75 mm or of Clark level II were of radial growth phase and that these melanomas rarely showed mitoses. They found no metastases in that group compared with melanomas with a vertical growth phase [19]. A thickness of ≤0·75 mm and Clark level II might thus be a good approximation of the radial growth phase. The 10-year melanoma-specific mortality rates for melanomas in SMR, QCR, NSW, SEER, CMMR and PLG for melanomas >0·75 mm are very similar (6·1-8·0%).

In all the reviewed studies except that of CMMR, ulceration is a poor prognostic sign. Unfortunately the large population-based QCR had no information on ulceration.

To further validate our data, we divided the data into nine groups from the expanded AJCC described by Gimotty [6]. Only minor differences were found in comparison with SEER data: head/neck tumours in SEER have higher mortality than in the SMR (SEER groups 3-4) and also SEER finds gender differences that are not apparent in the SMR (SEER group 5-6).

-Insert Table 5 about here-

We have identified three prognostic groups; a low risk group (67·9% of T1 cases), an intermediate risk group (28·6% of T1 cases), and a high risk group (3·5% of T1 cases). The latter has a slightly higher mortality rate than T2a tumours in a national report from the SMR, 1990-2008 [20]. Further subdivision of the SMR data would be possible but we chose to stay with division based on the most important factors from the multivariate analysis. We are aware that in the AJCC 2009 classification, mitoses have been added as an important prognostic factor [2] and other studies supports this [4,6]. A limitation in the present study is that we could not directly compare our results with AJCC 2009 data. From 2009, the SMR contains information on presence/absence of mitosis but before 2009 information on mitosis was not reported regularly. In the future, this data will be analysed against long-term mortality in order to determine whether adding mitosis as a prognostic factor can further improve risk stratification in this patient population.

In all the analyses from the SMR, patients were censored at the time point of a new melanoma diagnosis, thus eliminating the risk of a second melanoma being the underlying risk for cause of death from melanoma. However this methodology was not used in the other studies. Omitting censoring at the second melanoma diagnosis however, changed the SMR results only marginally; the 10-year melanoma-specific mortality rate increased by 0·3% (from 3·4% to 3·7%) in the total study cohort and there was no alteration regarding the outcome with respect to prognostic factors. In the SMR, eight cases of Clark level V were used in the multivariate analysis and this may indicate that these patients could have had thicker melanomas than what was actually registered. Only two of these were classified into the high risk group, one of whom died from the melanoma. Excluding the cases with Clark level V did not change the results in the multivariate Cox analysis. Five cases with positive sentinel node studies were identified, but none of those patients were classified into the high risk group. In the multivariate Cox analysis for T1, we tested two alternative ways of including tumour thickness. We tested if the Cox-model was improved by using four different tumour groups or by using a continuous thickness variable. None of these models

added significant additional information (*p*-values 0·32 and 0·04 respectively) and we therefore choose to stay with the three group model. Tumour thickness with three groups is also the most common way of dealing with this variable in other studies and this facilitates comparisons.

It is important to have the possibility to give patients with thin melanoma more accurate prognostic information. In Sweden thin melanomas constitute more than 50% (even higher for females and younger patients) of all melanomas. The prognosis is very good in average compared to other stages of melanoma and other cancer types, but we found a mortality range of 1-25% showing the importance of using prognostic factors. In the SMR, the high risk group (3·5% of T1) accounts for 15% of all melanoma deaths, and the intermediate group (28·6% of T1) accounts for 51% of all melanoma deaths. Using the old AJCC-2002 classification on SMR data, 12% of the patients were classified into T1b accounting for 31% of melanoma deaths. Our findings thus predict 66% of all melanoma deaths compared to 31% from conventional T1b.

In conclusion, using a population-based melanoma register and combining ulceration, tumour thickness and Clark's level of invasion three distinct prognostic subgroups were identified. Meta-analyses of population-based melanoma registers may be a method to further improve the risk stratification in this patient group.

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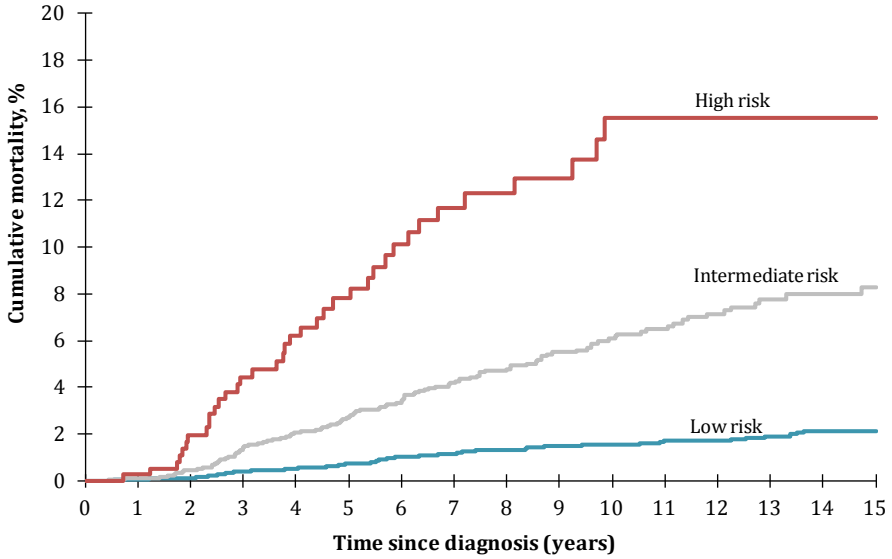
Figure legends

Fig.1. Cumulative melanoma-specific mortality by group

Low risk group: Non-ulcerated ≤0·75 mm & Clark II-III
Intermediate risk group: Non-ulcerated >0·75 mm; or non-ulcerated & Clark IV-V; or ulcerated ≤0·75 mm & Clark II
High risk group: Ulcerated & Clark III-V; or ulcerated >0·75 mm & Clark II



Patients at risk			
High risk:	212	92	27
Intermediate risk:	1852	937	304
Low risk:	4614	2382	874
Cumulative mortality (95% CI):			
High risk:	7·8 (5·3-11·5)	15·6 (11·2-21·4)	15·6 (11·2-21·4)
Intermediate risk:	2·7 (2·1-3·4)	6·1 (5·0-7·3)	8·3 (6·8-10·0)
Low risk:	0·7 (0·5-1·0)	1·5 (1·2-1·9)	2·1 (1·7-2·7)

Tables

Table 1 Melanoma-Specific Mortality Rates (1990-2008)

Variable	n	No. Melanoma Deaths (%)	Mortality (95% CI) 5-year	10-year	15-year
All Patients	13 026	311 (2·4)	1·7 (1·4-1·9)	3·4 (3·0-3·8)	4·4 (3·9-5·0)
Gender					
Men	5890	157 (2·7)	1·9 (1·5-2·4)	3·8 (3·2-4·6)	5·1 (4·1-6·2)
Women	7136	154 (2·2)	1·3 (1·0-1·7)	2·9 (2·4-3·6)	3·8 (3·1-4·6)
Age group					
0-44	3288	62 (1·9)	1·1 (0·8-1·6)	2·3 (1·7-3·1)	3·1 (2·4-4·0)
45-64	5233	125 (2·4)	1·5 (1·2-1·9)	3·1 (2·6-3·8)	4·5 (3·6-5·5)
65-79	3399	91 (2·7)	1·9 (1·4-2·5)	4·4 (3·5-5·5)	5·6 (4·4-7·2)
80+	1106	33 (3·0)	4·1 (2·8-5·9)	5·2 (3·7-7·5)	5·2 (3·7-7·5)
Tumour site					
Head/neck	1401	48 (3·4)	3·5 (2·5-4·9)	5·5 (4·0-7·6)	6·7 (4·8-9·2)
Upper extremities	2137	40 (1·9)	1·3 (0·8-1·9)	2·6 (1·8-3·7)	3·7 (2·6-5·3)
Lower extremities	3021	53 (1·8)	1·0 (0·7-1·5)	2·5 (1·8-3·3)	3·1 (2·3-4·1)
Trunk	6336	159 (2·5)	1·6 (1·3-2·0)	3·5 (2·9-4·1)	4·7 (3·9-5·6)
Palm/subungual	94	10 (10·6)	7·3 (3·3-15·6)	11·1 (5·6-21·4)	20·2 (9·4-40·3)
Missing	37	1 (2·7)	3·1 (0·4-20·2)	3·1 (0·4-20·2)	3·1 (0·4-20·2)
Histogenetic type					
SSM	10 256	217 (2·1)	1·4 (1·1-1·6)	3·0 (2·6-3·5)	3·9 (3·4-4·6)
LMM	1094	21 (1·9)	1·6 (0·9-2·8)	2·4 (1·4-4·1)	4·8 (2·7-8·6)
NM	403	25 (6·2)	5·4 (3·5-8·5)	8·5 (5·7-12·7)	9·3 (6·2-13·8)
ALM	90	7 (7·8)	3·7 (1·2-11·0)	7·4 (3·1-17·4)	16·2 (6·8-36·0)
Other types	1101	36 (3·3)	2·7 (1·7-4·0)	5·1 (3·5-7·2)	6·0 (4·2-8·7)
Missing	82	5 (6·1)	5·4 (2·1-13·9)	5·4 (2·1-13·9)	5·4 (2·1-13·9)
Tumour thickness, mm					
≤0·25	753	11 (1·5)	0·8 (0·3-2·0)	1·9 (1·0-3·7)	3·2 (1·6-6·4)
0·26-0·50	5080	59 (1·2)	0·9 (0·7-1·3)	1·4 (1·1-1·9)	2·0 (1·4-2·7)
0·51-0·75	3565	75 (2·1)	1·3 (0·9-1·7)	3·1 (2·4-3·9)	3·8 (3·0-4·9)
>0·75	3628	166 (4·6)	3·2 (2·6-4·0)	6·6 (5·6-7·8)	8·9 (7·5-10·6)
Clark's level of invasion					
II	6836	88 (1·3)	0·8 (0·6-1·1)	1·6 (1·2-2·0)	2·5 (1·9-3·2)
III	5022	164 (3·3)	2·3 (1·9-2·9)	4·9 (4·2-5·8)	6·4 (5·3-7·6)
IV-V	1036	53 (5·1)	3·7 (2·6-5·2)	7·2 (5·4-9·6)	8·5 (6·4-11·4)
Missing	132	6 (4·5)	4·5 (1·9-10·4)	6·0 (2·7-13·3)	6·0 (2·7-13·3)
Ulceration					
No	10 948	226 (2·1)	1·4 (1·2-1·7)	3·0 (2·6-3·4)	4·0 (3·5-4·7)
Yes	551	49 (8·9)	7·2 (5·2-10·1)	13·0 (9·7-17·2)	13·6 (10·2-17·9)
Missing	1527	36 (2·4)	1·6 (1·0-2·4)	2·6 (1·8-3·9)	4·1 (2·8-6·2)
T-stage (AJCC 2002)					
T1a	10 019	186 (1·9)	1·2 (1·0-1·5)	2·6 (2·2-3·1)	3·7 (3·1-4·3)
T1b	1508	89 (5·9)	4·5 (3·4-5·8)	8·5 (6·9-10·6)	9·6 (7·7-12·0)
Unclassifiable	1499	36 (2·4)	1·6 (1·1-2·5)	2·9 (2·0-4·2)	4·1 (2·7-6·0)

Table 2 Univariate- and Multivariate Cox Analysis, 1990-2008 (N = 11 165)

			Univariate				Multivariate			
Variable	**n**	**No. Melanoma Deaths (%)**	**HR**	**95% CI**	**χ2**	***P***	**HR**	**95% CI**	**χ2**	***P***
Gender					7·5	0·006			3·0	0.09
Men	5078	133 (2·6)	1·00				1·00			
Women	6087	120 (2·0)	0·71	0·55-0·91			0·79	0·61-1·03		
Age group					15·8	< 0·001			8·6	0·01
15-44	2867	55 (1·9)	1·00				1·00			
45-64	4492	101 (2·2)	1·30	0·94-1·81			1·19	0·86-1·66		
65-89	3806	97 (2·5)	1·91	1·37-2·66			1·63	1·15-2·30		
Tumour site					13·8	0·001			10·9	0·004
Extremities	4428	82 (1·9)	1·00				1·00			
Head/neck	1159	37 (3·2)	2·09	1·41-3·08			2·03	1·33-3·09		
Trunk	5578	134 (2·4)	1·28	0·98-1·69			1·28	0·96-1·71		
Histogenetic type					28·8	< 0·0001			8·7	0·03
SSM	9058	185 (2·0)	1·00				1·00			
LMM	909	18 (2·0)	1.18	0·73-1·92			0·91	0·53-1·56		
NM	336	21 (6·3)	3·06	1·95-4·80			1·64	1·04-2·60		
Other types/missing	862	29 (3·4)	1·77	1·19-2·61			1·55	1·05-2·30		
Tumour thickness, mm					103·2	< 0·0001			29·4	< 0·0001
≤0·5	5023	52 (1·0)	1·00				1·00			
0·51-0·75	3072	60 (2·0)	1·86	1·28-2·69			1·49	1·00-2·21		
>0·75	3070	141 (4·6)	4·71	3·43-6·47			2·76	1·86-4·08		
Clark's level of invasion					74·6	< 0·0001			12·3	0·002
II	6013	74 (1·2)	1·00				1·00			
III	4272	134 (3·1)	2·79	2·10-3·71			1·59	1·14-2·23		
IV-V	880	45 (5·1)	4·37	3·02-6·33			2·13	1·38-3·27		
Ulceration					83·2	< 0·0001			46·7	< 0·0001
No	10637	208 (2·0)	1·00				1·00			
Yes	528	45 (8·5)	4·48	3·25-6·19			3·16	2·27-4·39		

HR: hazard ratio; 95% CI: 95 % confidence interval.

Table 3 10-Year Melanoma-Specific Mortality Rates by Ulceration, Clark's Level of Invasion and Tumour Thickness, 1990-2008 (N=11 165)

Clark level/Tumour thickness	Ulceration			
	No		Yes	
	n (%)	Mortality (95% CI)	n (%)	Mortality (95% CI)
Clark level II				
≤0·5 mm	4072 (36·5)	0·9 (0·6-1·4)	93 (0·8)	7·0 (2·9-16·6)
0·51-0·75 mm	1302 (11·7)	1·6 (0·9-2·9)	46 (0·4)	5·8 (1·5-21·7)
>0·75 mm	452 (4·1)	5·0 (2·8-9·0)	48 (0·4)	13·3 (3·5-43·6)
Clark level III				
≤0·5 mm	744 (6·6)	2·0 (1·0-4·1)	26 (0·2)	17·4 (4·2-57·2)
0·51-0·75 mm	1463 (13·1)	3·0 (2·0-4·4)	73 (0·7)	12·5 (5·7-26·2)
>0·75 mm	1798 (16·1)	6·2 (4·8-7·9)	168 (1·5)	14·7 (8·8-23·9)
Clark level IV-V				
≤0·5 mm	78 (0·7)	4·0 (1·0-16·0)	10 (0·1)	11·1 (1·6-56·7)
0·51-0·75 mm	180 (1·6)	6·5 (2·9-14·1)	8 (0·1)	25·0 (6·9-68·5)
>0·75 mm	548 (4·9)	6·6 (4·4-10·0)	56 (0·5)	24·0 (11·6-45·6)

Table 4 10-Year Melanoma-Specific Mortality Rates from Previously Published Studies

	Population-based				Single-Institutional		Multi-Institutional		
Study	**Current study**	**QCR**	**SEER**	**NSW**	**PLG**	**SMU**	**CMMR**	**AJCC 2002**	**AJCC 2009**
Period	1990-2008	1982-2006	1998-2001	1983-1998	1972-2001	1979-1998	1976-2000	1976-2000	1976-2008
No. Patients	13 026	26 736	26 291	18 088	2389	2746	12 728	5890	11 841
Median age (years)	58	52·7 (mean)	-	54	-	45·9	50 (mean)	-	-
Median thickness (mm)	0·60	-	0·46 (mean)	0·50	0·53 (mean)	0·60	0·57	-	-
% T1a (AJCC 2002)	87%	-	90%	-	84%	-	-	77%	80%[a]
All T1	3·4%	2·6%	3·3%[b]	3·6%	3·5%[b]	7·3%	3·5%	13·0%[b]	8·0%
T1a (AJCC 2002)	2·6%	-	2·6%	-	2·8%	-	-	12·1%	7-8%[a]
T1b (AJCC 2002)	8·5%	-	9·8%	-	7·4%	-	-	16·9%	12-13%[a]
≤0·75 mm	1·9-3·1%	1·3-2·5%	-	2·3-2·7%	-	-	2·3-3·6%	-	-
>0·76 mm	6·6%	6·8%	7%	7%	8%	-	6·1%	-	-
Non-ulcerated	3·0%	-	-	-	-	7·7%	3·5%	14%	5%
Ulcerated	13·0%	-	-	-	-	16%	4·1%	24%	12%

[a]According to AJCC 2009 classification, [b]Calculated value from T1a and T1b

Table 5 10-Year Melanoma-Specific Mortality Rates Using Expanded AJCC (SEER)

	Mortality	
Expanded AJCC Groups	**Current study**	**SEER**
1: No ulceration, ≤0·78 mm, Clark level II, <60 years	0·9	1·0
2: No ulceration, ≤0·78 mm, Clark level II, ≥60 years	1·4	2·5
3: No ulceration, ≤0·78 mm, Clark level III, other sites	2·6	3·2
4: No ulceration, ≤0·78 mm, Clark level III, head/neck	4·3	7·9
5: No ulceration, >0·78 mm, Clark level III, women	5·7	4·4
6: No ulceration, >0·78 mm, Clark level III, men	6·3	9·4
7: No ulceration, Clark level IV-V	6·3	8·6
8: Ulceration, Clark level II-III	11·4	11·1
9: Ulceration, Clark level IV-V	22·4	30·2